Cardiopulmonary bypass and hemostasis

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SUMMARY

In chapter I, we recalled that intracardiac defects can only be corrected when cardiopulmonary circulation is maintained by extracorporeal circulation and ventilation. To prevent clot formation in this artificial circuit, the so-callled cardiopulmonary bypass (CPB), we completely depend on the anticoagulatory properties of heparin. Heparin inhibits the clotting system, which is triggered via the intrinsic pathway by blood-material interaction. Blood-material interaction also activates the kinin, plasmin, and complement systems. These systems are all part of the host defense mechanism where platelets and leucocytes are instrumental in maintaining local hemostasis and preventing infiltration by micro-organisms. During CPB, foreign surfaces activate these systems massively and systemically. This activation induces the so-called whole body inflammatory response (WBIR), which frequently results in impaired hemostasis and organ dysfunction.

Since 1985, we have been performing clinical studies on the WBIR at the Onze Lieve Vrouwe Gasthuis (OLVG) in Amsterdam in co-operation with the research division of the Department of Cardiopulmonary Surgery in Groningen. To evaluate the process of impaired hemostasis experienced in cardiac surgery on an every-day basis, first the basic mechanisms of hemostasis have to be understood. For this reason, recent textbooks and keynote articles have been studied (chapter II), our results of clinical studies done in the past have been re-analysed (chapter III and IV and addendum), and the interpretation of results obtained in our recent clinical studies (chapter V, VI and VII) are presented. By this process of evaluation, a novel view on the hemostatic alterations and modifications in CPB was developed.

In chapter II, the hemostatic mechanisms relevant for the cardiac surgeon were described. Hemostasis is regulated locally by the concerted action of vessel wall, platelets, and activated plasmatic systems. This action is regulated by thrombin, which is the back bone of hemostasis. Exposure of subendothelium caused by vessel wall damage initiates a hemostatic process in the following sequence.

By means of its adhesive receptor (GPIb) and via the vWF, platelets adhere to the subendothelium. Subendothelium releases tissue factor and activates the extrinsic clotting pathway. The first traces of thrombin bind to the GPIb receptor. The thus activated platelet expresses its GPIIbIIIa receptor, which will bind fibrinogen so that aggregation takes place. Another

action of thrombin is cleaving fibrinogen into fibrin, resulting in the formation of a consolidated hemostatic plug. This process is balanced by fibrinolysis. Consequently, hemostatic plug formation is restricted to the site of the vessel wall damage only.

During CPB, the sequence of the above-described process is different. Traces of thrombin are generated via contact-induced intrinsic clotting, despite systemic heparinzation. Because thrombin has a higher affinity for GPIb than for fibrinogen, these traces primarily bind and cleave platelet adhesive receptors, thus affecting the hemostatic function of platelets. The GPIIbIIIa receptor simultaneously expressed by thrombin is also capable of binding to vWF and may (partly) serve as a back-up mechanism for platelet adhesion. However, this is no compensation for the massive functional decrease of GPIb.

In chapter III, the alterations in hemostasis during CPB were described. We re-analyzed the biochemical data collected for various clinical studies that we did in the past. First, two phases of increased fibrinolytic activity were observed: one in conjunction with heparin administration, another after releasing the aortic cross clamp. The observations of blood oozing in a "dry" operation field after heparin administration and heparin enhancing fibrinolytic activity are already sufficient to necessitate the search for better anticoagulants. More importantly, we noticed that despite high systemic heparinization thrombin generation is not completely blocked.

Therefore, the observed decrease of GPIb receptors immediately after the onset of CPB could, indeed, be caused by thrombin generation. The increase of a specific molecular marker for disseminated intravascular coagulation (DIC) right from the start of CPB indicates that this pattern, modified by the presence of heparin, should be regarded as the initiation of an acute DIC process.

In chapter IV, previous results of our study on the effect of the antiprotease aprotinin on hemostasis in CPB were reviewed. Next to its known antifibrinolytic effect, aprotinin has a synergistic effect with heparin on the intrinsic clotting and prevents thrombin generation by contact activation. In the presence of aprotinin, the specific marker for DIC was completely inhibited, GPIb platelet receptors were preserved, and hemostasis improved. *These effects suggest once more the prominent role of thrombin in the process towards affected hemostasis during CPB.* Since 2.10^6 KIU of aprotinin added to the pump prime is enough to inhibit thrombin generation, to preserve GPIb platelet receptors, and to improve hemostasis, the initial

recommended 6.10^6 KIU high continuous dose scheme is redundant. Moreover, because the antifibrinolytic effect of aprotinin disturbs the physiological balance between fibrinolysis and clotting, there is a danger of clot formation when aprotinin is given during periods when patients are not anticoagulated as happens when the 6.10^6 KIU dose scheme is adopted.

In chapter V, the protocol of two recent studies was described.

In chapter VI, the hemostatic effect of ASA treatment with and without aprotinin was evaluated. Patients receiving ASA showed significantly increased platelet degranulation and further impairment of platelet function during CPB. In ASA-treated patients, aprotinin prevented both these effects. In addition, aprotinin preserved GPIb platelet receptors and improved hemostasis equally well in ASA-treated patients as in non-ASA-treated patients. Therefore, thrombin is likely the common agonist that causes both the excessive platelet release reaction and the additional impairment of platelet function in ASA-treated patients.

In chapter VII, the possible role of the thrombin-platelet interaction in blood loss during CPB was further evaluated. We observed that patients whose pre-operative platelet numbers were higher than the 50th percentile lost significantly less blood than patients with lower numbers. Aprotinin treatment only significantly reduced blood loss in patients with the lower platelet numbers. Our interpretation is that under systemic heparinization a limited amount of thrombin is generated which will affect a limited number of platelets.

When relatively high pre-operative platelet numbers are available, sufficient unaffected platelets persist to maintain normal hemostasis but not when a patient has a low platelet number to start with. However, in the situation where aprotinin is administered, inhibition of thrombin generation will preserve the platelet adhesive function and thus hemostasis.

By varying the timing of aprotinin administration, we tried to further pinpoint the mechanism of its effect on hemostasis.

Administering similar doses of aprotinin during the entire pre-CPB period, or a single dose synchronous with heparin administration, or a dose only to the pump prime, all caused a similarly significant reduction in post-operative blood loss. This is consistent with the hypothesis that aprotinin acts via its synergistic effect on the inhibition of intrinsic clotting that is caused by contact activation induced by the heart-lung machine.